

alpha linkage between the first protected saccharide and the second protected saccharide,

wherein the first protected saccharide is selected from the group consisting of a D-glucosamine unit and an oligosaccharide comprised of alternating D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal D-glucosamine at the reducing end, and

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wherein the second protected saccharide is selected from the group consisting of a uronic acid unit and an oligosaccharide comprised of alternating D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal uronic acid at the non-reducing end, further

wherein any uronic acid unit is selected from the group consisting of D-glucuronic acid and L-iduronic acid and further

wherein any D-glucosamine units have nitrogen containing groups at carbon 2, which nitrogen containing groups can be treated to form an amine.

2  
~~142.~~ A process for synthesizing a protected heparinic condensation product having from 2 - 12 saccharide units and having semi-permanent protecting groups and permanent protecting groups as substituents at carbon positions thereon to allow selective positioning of functional groups at desired positions, and further having other protecting groups which form an ester at carboxyl groups, and having nitrogen containing groups as substituents at position 2 of D-glucosamine units, which process

comprises the step of condensing a first protected saccharide with a second protected saccharide to form a protected condensation product,

I wherein the first protected saccharide is selected from the group consisting of a protected D-glucosamine unit and an oligosaccharide comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal D-glucosamine at the reducing end, further wherein the first protected saccharide has a reactive group as a substituent at carbon 1 at the reducing end which reactive group allows a stereospecific linkage during the condensation, and

wherein the second protected saccharide is selected from the group consisting of a protected uronic acid unit and an oligosaccharide comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal uronic acid at the nonreducing end, wherein any uronic acid units are selected from the group consisting of D-glucuronic acid and L-iduronic acid, and

wherein the protected condensation product formed has a 1-4 alpha linkage between the first protected saccharide and the second protected saccharide, the protected condensation product further having at least one each of semi-permanent protecting groups, permanent protecting groups, other protecting groups, and nitrogen containing groups as substituents at carbon positions thereon which protecting groups and nitrogen containing groups were present on the first protected saccharide and second protect-

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ed saccharide, which semi-permanent protecting groups are removable in the presence of permanent protecting groups, are stable during the condensation, and allow a stereospecific linkage during the condensation, which permanent protecting groups are stable and do not migrate to different carbon positions during the removal of the semi-permanent protecting groups and the introduction of functional groups to replace the semi-permanent protecting groups, which functional groups are selected from the group consisting of  $-O-SO_3$  groups and  $-O-PO_3$  groups, and which permanent protecting groups also are removable in the presence of the functional groups, are stable during the condensation, and allow a stereospecific linkage during the condensation, and which other protecting groups form an ester at the carboxyl group of the uronic acid units and are stable during the condensation, and which nitrogen containing groups are substituents at carbon 2 of the D-glucosamine units, can be treated to form an amine, are stable during the condensation, and allow a stereospecific linkage during the condensation.

3  
~~143.~~ A process for synthesizing a protected heparinic condensation product having from 2 - 12 saccharide units and having semi-permanent protecting groups and permanent protecting groups as substituents at carbon positions thereon to allow selective positioning of functional groups at desired positions, further having other protecting groups which form an ester at the carboxyl groups, and nitrogen containing groups as substituents

at carbon positions thereon, which process comprises condensing a first protected saccharide with a second protected saccharide to form a protected condensation product

I / wherein the first protected saccharide is selected from the group consisting of a protected uronic acid unit and an oligosaccharide comprised of alternating D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal uronic acid at the reducing end, further wherein the first protected saccharide has a reactive group as a substituent at carbon 1 at the reducing end which reactive group allows the condensation to occur and which allows a stereospecific linkage during the condensation, and

wherein the second protected saccharide is selected from the group consisting of a protected D-glucosamine unit and an oligosaccharide comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal D-glucosamine at the nonreducing end, wherein any uronic acid units are selected from the group consisting of D-glucuronic acid and L-iduronic acid, and wherein the protected condensation product formed has a 1-4 beta linkage between the first protected saccharide and the second protected saccharide where the first protected saccharide is a D-glucuronic acid or an oligosaccharide having a terminal D-glucuronic acid, and wherein the protected condensation product formed has a 1-4 alpha linkage between the first protected saccharide and the second protected saccharide where the first protected saccharide is an L-iduronic

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acid or an oligosaccharide having a terminal L-iduronic acid, the protected condensation product further having at least one each of semi-permanent protecting groups, permanent protecting groups, other protecting groups, and nitrogen containing groups as substituents at carbon positions thereon which protecting groups and nitrogen containing groups were present on the first protected saccharide and second protected saccharide, which semi-permanent protecting groups are removable in the presence of permanent protecting groups, are stable during the condensation, and allow a stereospecific linkage during the condensation, which permanent protecting groups are stable and do not migrate to different carbon positions during the removal of semi-permanent protecting groups and the introduction of functional groups to replace the semi-permanent protecting groups, which functional groups are selected from the group consisting of  $-O-SO_3$  groups and  $-O-PO_3$  groups, and which permanent protecting groups also are removable in the presence of the functional groups, are stable during the condensation, and allow a stereospecific linkage during the condensation, and which other protecting groups form an ester at the carboxyl groups of the uronic acid units, and are stable during the condensation, and which nitrogen containing groups comprise nitrogen containing groups at carbon 2 of the D-glucosamine units, which nitrogen containing groups can be treated to form an amine, are stable during the condensation, and allow a stereospecific linkage during the condensation.

~~144.~~ A process for synthesizing a protected heparinic condensation product having from 2 - 12 saccharide units and having semi-permanent protecting groups and permanent protecting groups as substituents at carbon positions thereon to allow selective positioning of functional groups at desired positions, further having other protecting groups which form an ester at the carboxyl groups and further having nitrogen containing groups at position 2 of D-glucosamine units which process comprises a first step of condensing a first protected saccharide with a second protected saccharide precursor to form a protected condensation product

wherein the first protected saccharide is selected from the group consisting of a protected uronic acid unit and an oligosaccharide comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal uronic acid at the reducing end, further wherein the first protected saccharide has a reactive group as a substituent at carbon 1 at the reducing end which reactive group allows a stereospecific linkage during the condensation, and

wherein the second protected saccharide is a glucose derivative which is a D-glucosamine precursor, which D-glucosamine precursor has one or more precursor groups as substituents which are selected from the group consisting of a 1, 6 anhydro group and a 2, 3 epoxy group, further wherein any uronic acid units are selected from the group consisting of D-glucuronic acid and L-iduronic acid, and

I' wherein the protected condensation product formed has a 1-4 beta linkage between the first protected saccharide and the second protected saccharide where the first protected saccharide is a D-glucuronic acid or an oligosaccharide having a terminal D-glucuronic acid, and wherein the protected condensation product formed has a 1-4 alpha linkage between the first protected saccharide and the second protected saccharide where the first protected saccharide is an L-iduronic acid or an oligosaccharide having a terminal L-iduronic acid, the protected condensation product further having protecting groups and precursor groups as substituents at carbon positions thereon, which protecting groups and precursor groups were present on the first and second protected saccharide,

further comprising the second step of treating any 1,6 anhydro precursor group to form semi-permanent protecting groups or permanent protecting groups at carbons 1 and 6 and treating any 2, 3 epoxy precursor group to form a semi-permanent protecting group or a permanent protecting group at carbon 3 and a nitrogen containing group at carbon 2, which semi-permanent protecting groups are removable in the presence of permanent protecting groups, and which permanent protecting groups are stable and do not migrate to different carbon positions during the removal of semi-permanent protecting groups and the introduction of functional groups to replace the semi-permanent protecting groups, which functional groups are selected from the group consisting of -O-SO<sub>3</sub> groups and -O-PO<sub>3</sub> groups, and which permanent protecting



groups also are removable in the presence of the functional groups, and which other protecting groups form an ester at the carboxyl groups of the uronic acid units and are stable during the condensation, and which nitrogen containing groups occupy carbon 2 of the D-glucosamine units, can be treated to form an amine, are stable during the condensation and allow a stereospecific linkage during the condensation.

*I*  
~~11~~ ~~145.~~ A process as in claim ~~142~~, ~~143~~ or ~~144~~ wherein the functional groups are -O-SO<sub>3</sub> groups.

~~12~~ ~~146.~~ A process as in claim ~~145~~ wherein the semi-permanent protecting groups are substituents at one or more carbon positions at any of carbons 3 and 6 of D-glucosamine units, and carbons 2 and 3 of uronic acid units, and wherein the permanent protecting groups are substituents at the carbons 3 and 6 of the D-glucosamine units and carbons 2 and 3 of the uronic acid units which are not occupied by the semi-permanent protecting groups.

~~13~~ ~~147.~~ The process of claim ~~146~~ wherein

a) The nitrogen containing groups are selected from the group consisting of

1. N<sub>3</sub>,
2. NH - lower acyl, and
3. NHCO - lower arylalkyl;



- b) the protecting groups which form an ester at the carboxyl are selected from the group consisting of
1. lower alkyl, and
  2. lower aryl;
- c) the semi-permanent protecting groups are -O-lower acyl;
- d) the permanent protecting groups are -O-benzyl; and
- e) the reactive group is selected from the group consisting of
1. halogen,
  2. O-lower imidoyl, and
  3. an orthoester formed between carbon 1 and carbon 2 of D-glucosamine.

14 13  
~~148.~~ The process of claim ~~147~~ wherein

- a) The nitrogen containing groups are selected from the group consisting of
1.  $N_3$ ,
  2. NH - acetyl, and
  3. NHCO - benzyl;
- b) the protecting groups which forms an ester at the carboxyl are methyl;
- c) the semi-permanent groups are -O-acetyl;
- d) the permanent protecting groups are -O-benzyl; and
- e) the reactive group is selected from the group consisting of

1. Br,
2. Cl,
3. an orthoester having between 3 and 6 carbons,  
and
4. C(NH)CCl<sub>3</sub>.

*I* ~~5~~ <sup>4</sup> 149. A process according to claim ~~144~~ wherein the second protected saccharide is a glucose derivative which is a D-glucosamine precursor which contains a 1, 6 anhydro group, wherein the 1, 6 anhydro group is treated with an acetolysing agent to obtain -O-acetyl semi-permanent protecting groups.

~~6~~ <sup>5</sup> 150. A process according to claim ~~149~~ wherein the D-glucosamine precursor also contains a 2, 3 epoxide group, wherein the 2, 3 epoxide group is opened with a nucleophile and the resulting OH is acetylated at the position 3 carbon to obtain an -O-acetyl semi-permanent protecting group at carbon 3 and an azide nitrogen containing group at carbon 2.

~~7~~ <sup>5</sup> 151. A process according to claim ~~149~~ wherein the D-glucosamine precursor also contains a 2, 3 epoxide group, wherein the 2, 3 epoxide group is opened with a nucleophile and the resulting OH is benzylated at the position 3 carbon to obtain an -O-benzyl permanent protecting group at carbon 3 and an azide nitrogen containing group at carbon 2.

~~8~~  
~~152~~. A process according to claim ~~150~~ or ~~151~~ wherein the nucleophile is sodium azide and the nitrogen containing group is  $N_3$ .

~~9~~  
~~153~~. A process according to claim ~~144~~ wherein the D-glucosamine unit contains a 1,6 anhydro group, comprising treating with an acetolysing agent in order to obtain an -O-acetyl group at carbon 1 of the D-glucosamine, further comprising the step of removing the acetyl group and replacing it with a reactive group in order to allow the protected condensation product to be elongated.

~~10~~  
~~154~~. A process according to claim ~~153~~ wherein the reactive group is selected from the group consisting of bromine and chlorine.

~~20~~  
~~155~~. A process as in claim ~~142~~ or ~~143~~ wherein the carbon 1 at the reducing end of the protected condensation product is occupied by a protecting group which is selected from the group consisting of a semi-permanent protecting group and a permanent protecting group.

~~21~~  
~~156~~. A process as in claim ~~142~~ or ~~143~~ wherein the carbon 4 at the non-reducing end of the protected condensation product is occupied by a protecting group which is selected from the group

consisting of a semi-permanent protecting group and a permanent protecting group.

~~22~~  
~~157~~. A process as in claim ~~142~~<sup>2</sup> or ~~143~~<sup>3</sup> further wherein the carbon 1 at the reducing end of the protected condensation product is occupied by an inert protecting group, which inert protecting group is stable during the condensation and during removal of the permanent protecting groups.

~~23~~  
~~158~~. A process for synthesizing a protected heparinic condensation product which can be elongated, having from 2 - 12 saccharide units and having semi-permanent protecting groups and permanent protecting groups as substituents at carbon positions thereon to allow selective positioning of functional groups at desired positions, and further having other protecting groups which form an ester at carboxyl groups, and having nitrogen containing groups as substituents at position 2 of D-glucosamine units, and further having temporary groups positioned thereon to allow elongation of the protected condensation product, which process comprises condensing a first protected saccharide with a second protected saccharide to form a protected condensation product

wherein the first protected saccharide is selected from the group consisting of a protected D-glucosamine unit and an oligosaccharide comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and

having a terminal D-glucosamine at the reducing end, further wherein the first protected saccharide has a reactive group as a substituent at carbon 1 at the reducing end which reactive group allows the condensation to occur and also allows a stereospecific linkage during the condensation, and


II wherein the second protected saccharide is selected from the group consisting of a protected uronic acid unit and an oligosaccharide comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal uronic acid at the nonreducing end, wherein any uronic acid is selected from the group consisting of D-glucuronic acid and L-iduronic acid, and

wherein the protected condensation product has a 1-4 alpha linkage between the first protected saccharide and the second protected saccharide, the protected condensation product further having at least one each of semi-permanent protecting groups, permanent protecting groups, temporary protecting groups, other protecting groups, and nitrogen containing groups as substituents at carbon positions thereon which protecting groups and nitrogen containing groups were present on the first protected saccharide and second protected saccharide, which semi-permanent protecting groups are removable in the presence of permanent protecting groups, are stable during the condensation, and allow a stereospecific linkage during the condensation, which permanent protecting groups are stable and do not migrate to different carbon positions during introduction of functional groups to

replace the semi-permanent protecting groups, which functional groups are selected from the group consisting of  $-O-SO_3$  groups and  $-O-PO_3$  groups, and which permanent protecting groups also are removable in the presence of the functional groups, are stable during the condensation, and allow a stereospecific linkage during the condensation, which other protecting groups form an ester at the carboxyl groups of the uronic acid units, and are stable during the condensation, which temporary protecting groups are substituents at any of carbon 1 at the reducing end of the protected condensation product and carbon 4 at the non-reducing end of the protected condensation product and are removable in the presence of the semi-permanent protecting groups and permanent protecting groups in order to permit elongation of the protected condensation product, and which nitrogen containing groups are substituents at carbon 2 of the D-glucosamine units, can be treated to form an amine, are stable during the condensation, and allow a stereospecific linkage during the condensation.

*24*  
~~159.~~ A process for synthesizing a protected heparinic condensation product which can be elongated, having from 2 - 12 saccharide units and having semi-permanent protecting groups and permanent protecting groups as substituents at carbon positions thereon to allow selective positioning of functional groups at desired positions, and further having other protecting groups which form an ester at carboxyl groups, and having nitrogen containing groups as substituents at position 2 of D-glucosamine

units, and further having temporary groups positioned thereon to allow elongation of the protected condensation product, which process comprises condensing a first protected saccharide with a second protected saccharide to form a protected condensation product

 wherein the first protected saccharide is selected from the group consisting of a protected uronic acid unit and an oligosaccharide comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal uronic acid at the reducing end, further wherein the first protected saccharide has a reactive group as a substituent at carbon 1 at the reducing end, which reactive group allows a stereospecific linkage during the condensation, and

wherein the second protected saccharide is selected from the group consisting of a protected D-glucosamine unit and an oligosaccharide comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having a terminal D-glucosamine at the nonreducing end, wherein any uronic acid is selected from the group consisting of D-glucuronic acid and L-iduronic acid, and

wherein the protected condensation product has a 1-4 beta linkage between the first protected saccharide and the second protected saccharide where the first protected saccharide is a D-glucuronic acid unit or an oligosaccharide having a terminal D-glucuronic acid, and a 1-4 alpha linkage between the first protected saccharide and the second protected saccharide where



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the first protected saccharide is an L-iduronic acid unit or an oligosaccharide having a terminal L-iduronic acid, the protected condensation product further having at least one each of semi-permanent protecting groups, permanent protecting groups, temporary protecting groups, other protecting groups, and nitrogen containing groups as substituents at carbon positions thereon which protecting groups and nitrogen containing groups were present on the first protected saccharide and second protected saccharide, which semi-permanent protecting groups are removable in the presence of permanent protecting groups, are stable during the condensation, and allow a stereospecific linkage during the condensation, which permanent protecting groups are stable and do not migrate to different carbon positions during introduction of functional groups to replace the semi-permanent protecting groups, which functional groups are selected from the group consisting of  $-O-SO_3$  groups and  $-O-PO_3$  groups, and which permanent protecting groups also are removable in the presence of the functional groups, are stable during the condensation, allow a stereospecific linkage during the condensation, which other protecting groups form an ester at the carboxyl groups of the uronic acid units and are stable during the condensation, which temporary protecting groups are substituents at any of carbon 1 at the reducing end of the protected condensation product and carbon 4 at the non-reducing end of the protected condensation product, and are removable in the presence of the semi-permanent protecting groups and permanent protecting groups in order to permit elongation of

the protected condensation product, and which nitrogen containing groups are substituents at carbon 2 of the D-glucosamine units, can be treated to form an amine, are stable during the condensation, and allow a stereospecific linkage during the condensation.

<sup>25</sup>  
~~160~~. A process as in claim <sup>23</sup>~~158~~ or <sup>24</sup>~~159~~ wherein the functional groups are -O-SO<sub>3</sub> groups.

<sup>26</sup>  
~~161~~. A process as in claim <sup>25</sup>~~160~~ wherein the semi-permanent protecting groups are substituents at one or more carbon positions at any of carbons 3 and 6 of D-glucosamine units, and carbons 2 and 3 of uronic acid units, and wherein the permanent protecting groups are substituents at the carbons 3 and 6 of the D-glucosamine units and carbons 2 and 3 of the uronic acid units which are not occupied by the semi-permanent protecting groups.

<sup>27</sup>  
~~162~~. A process according to claim <sup>26</sup>~~161~~ further comprising the steps of removing a temporary protecting group at carbon one at the reducing end of the protected condensation product, substituting a reactive group and performing a second condensation to form an elongated protected condensation product comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having protecting groups thereon.

28  
163. A process according to claims 161 further comprising the steps of removing the temporary group at carbon 4 of the non-reducing end of the protected condensation product and performing a second condensation to form an elongated condensation product comprised of alternating protected D-glucosamine and uronic acid units linked in the manner found in heparin and having protecting groups thereon.

29  
164. The process of claim 161 wherein

- 26
- a) The nitrogen containing groups are selected from the group consisting of
1.  $N_3$ ,
  2.  $NH$  - lower acyl, and
  3.  $NHCO$  - lower arylalkyl;
- b) the protecting groups at the carboxyl are selected from the group consisting of
1. lower alkyl, and
  2. lower aryl;
- c) the semi-permanent protecting groups are -O-lower acyl;
- d) the permanent protecting groups are -O-benzyl; and
- e) the reactive group is selected from the group consisting of
1. halogen,
  2. -O-lower imidoyl, and

3. an orthoester formed between carbon 1 and carbon 2 of D-glucosamine;

f) the temporary group is selected from the group consisting of

1. -O-lower acyl,
2. -O-allyl,
3. -O-propenyl,
4. halogenated -O-lower acyl, and
5. -O-p-methoxy benzoyl.

*II* <sup>30</sup>  
~~165~~. The process of claim ~~164~~ wherein

a) The nitrogen containing groups are selected from the group consisting of

1.  $N_3$ ,
2. NH - acetyl, and
3. NHCO - benzyl;

b) The protecting groups which forms an ester at the carboxyl are methyl;

c) The semi-permanent groups are -O-acetyl;

d) The permanent protecting groups are -O-benzyl; and

e) the reactive group is selected from the group consisting of

1. Br,
2. Cl,
3. an orthoester having between 3 and 6 carbons, and

4.  $\left[ \text{C}(\text{NH})\text{CCl}_3; \right]$

f) The temporary protecting groups are selected from the group consisting of

1. -O-acetyl,
2. -O-allyl,
3. -O-propenyl,
4. monochloro-O-acetyl,
5. trichloro-O-acetyl, and
6. -O-p-methoxy benzoyl.

*II*

~~31~~  
~~166.~~ A process for selectively positioning sulfate groups or phosphate groups on a protected heparinic polysaccharide having from 2-12 units, which polysaccharide is comprised of alternating D-glucosamine and uronic acid units linked in the manner found in heparin and having at least one each as substituents of semi-permanent protecting groups, permanent protecting groups other protecting groups which form an ester at the carboxyl groups of the uronic acid units, and nitrogen containing groups at carbon 2 of the D-glucosamine units, wherein the permanent protecting groups are stable and do not migrate to other carbon positions during removal of the semi-permanent protecting groups and the introduction of functional groups, and wherein any uronic acid units are selected from the group consisting of D-glucuronic acid and L-iduronic acid, which process comprises the steps of

a) removing the semi-permanent protecting groups,

- b) introducing functional groups in place of the semi-permanent protecting groups, which functional groups are selected from the group consisting of  $-O-SO_3$  groups and  $-O-PO_3$  groups, and
- c) removing the permanent protecting groups and converting the nitrogen containing group into an amine group.

*II* <sup>32</sup>  
~~167~~. A process as in claim ~~166~~<sup>31</sup> wherein the functional groups are  $-O-SO_3$  groups.

<sup>33</sup>  
~~168~~. A process as in claim ~~167~~<sup>32</sup> wherein the semi-permanent protecting groups are substituents at one or more carbon positions at any of carbons 3 and 6 of D-glucosamine units, and carbons 2 and 3 of uronic acid units, and wherein the permanent protecting groups are substituents at the carbons 3 and 6 of the D-glucosamine units and carbons 2 and 3 of the uronic acid units which are not occupied by the semi-permanent protecting groups.

<sup>34</sup>  
~~169~~. The process of claim ~~168~~<sup>33</sup> wherein

a) The nitrogen containing groups are selected from the group consisting of

1.  $N_3$ ,
2.  $NH$  - lower acyl, and
3.  $NHCO$  - lower arylalkyl;

b) the protecting groups at the carboxyl are selected from the group consisting of

1. lower alkyl, and
2. lower aryl;

c) the semi-permanent protecting groups are -O-lower acyl; and

d) the permanent protecting groups are -O-benzyl.

*35*  
*II* ~~170~~. The process of claim ~~169~~ wherein *34*

a) The nitrogen containing groups are selected from the group consisting of

1.  $N_3$ ,
2. NH - acetyl, and
3. NHCO - benzyl;

b) The protecting groups which forms an ester at the carboxyl are methyl;

c) The semi-permanent groups are -O-acetyl; and

d) The permanent protecting groups are -O-benzyl.

*36*  
~~171~~. A process as in claim ~~166~~ further comprising the step of substituting the amine group with a group selected from the group consisting of  $SO_3$  and acyl. *31*

*37*  
~~172~~. A process as in claim ~~171~~ wherein the amine group is substituted with a group selected from the group consisting of  $SO_3$  and acetyl. *36*



~~38~~ 173. A process as in claim ~~172~~ <sup>37</sup> further comprising removing the protecting groups at the carboxyl groups of the uronic acid units.

~~39~~ 174. The process of claim ~~173~~ <sup>38</sup> which further comprises salifying the  $\text{COO}^-$  with an alkaline metal cation.

~~40~~ 175. The process of claim ~~174~~ <sup>39</sup> wherein the semi-permanent protecting groups are acetyl and are hydrolysed with a strong base followed by reaction with a sulfation agent.

~~41~~ 176. The process of claim ~~175~~ <sup>40</sup> wherein following introduction of the functional group  $-\text{O}-\text{SO}_3$  the compound formed is purified by fractionation.

~~42~~ 177. The process of claim ~~176~~ <sup>41</sup> wherein following fractionation of the compound, the compound is passed through a sodium ion exchange column.

~~15~~ 178. The process of claim ~~177~~ <sup>13</sup> wherein the condensation reaction is between a halide and an OH and is carried out in a solvent medium in the presence of a catalyst.

~~16~~ 179. The process of claim ~~178~~ <sup>15</sup> wherein the solvent is an organic solvent selected from the group consisting of dichloro-

methane and dichloroethane and the catalyst is selected from the group consisting of a silver and a mercury salt.

~~17~~ <sup>16</sup> 180. The process of claim ~~179~~ wherein the catalyst is selected from the group consisting of trifluoromethane, silver carbonate, silver oxide, mercuric bromide and mercuric cyanide.

~~18~~ <sup>3 4</sup> 181. The process of claim ~~143~~ or ~~144~~ wherein the reactive group is 1,2-O-methoxyethylidene, and the condensation is carried out in a solvent which boils above 100 degrees centigrade in the presence of a catalyst.

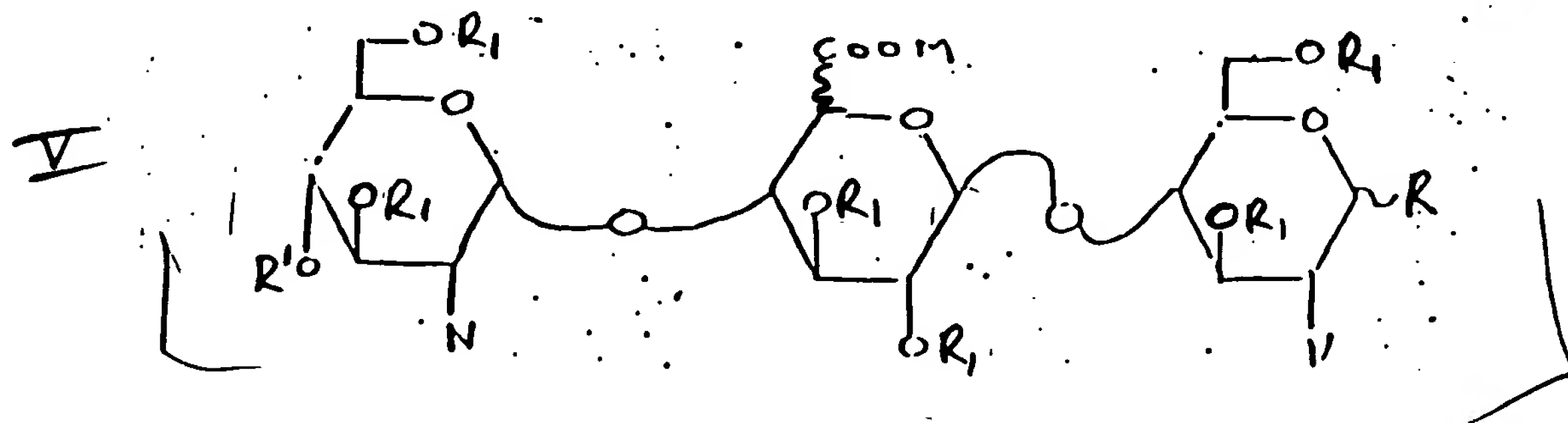
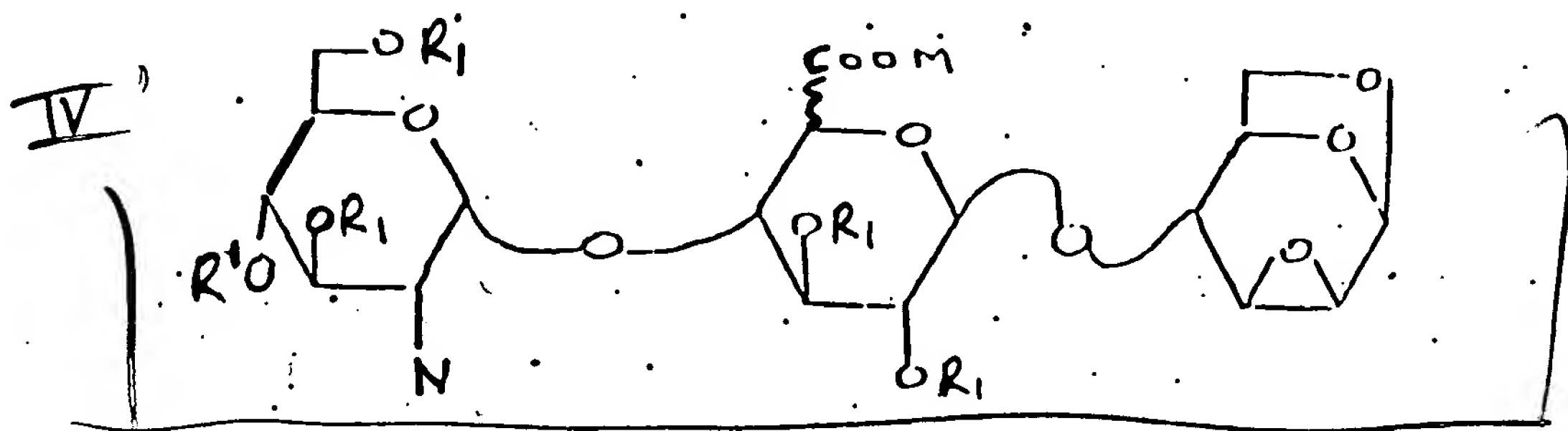
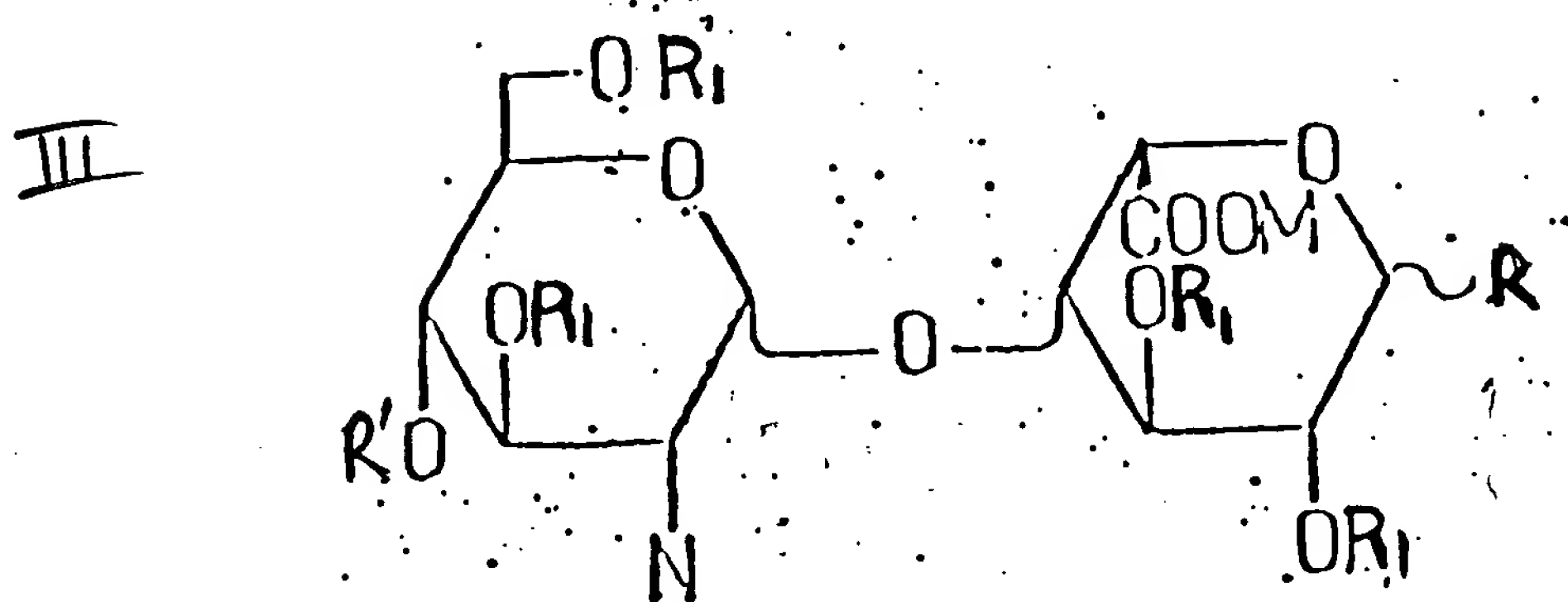
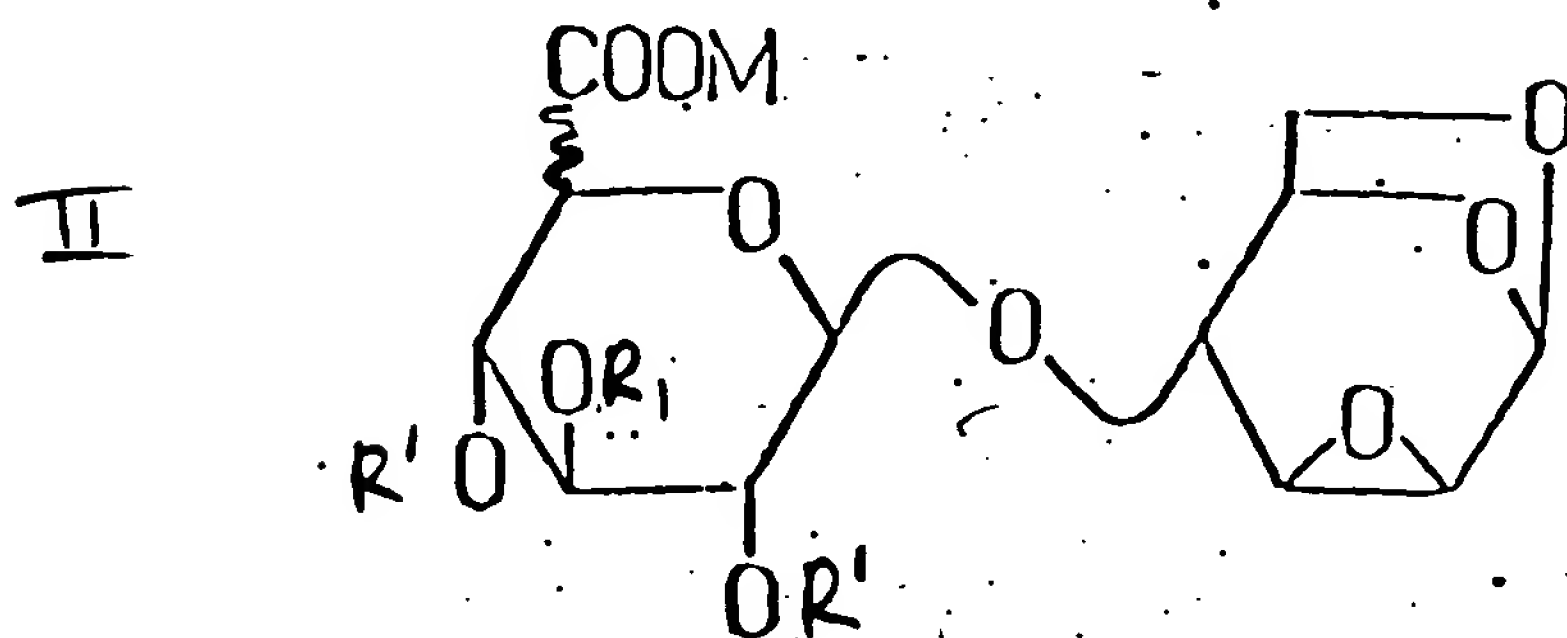
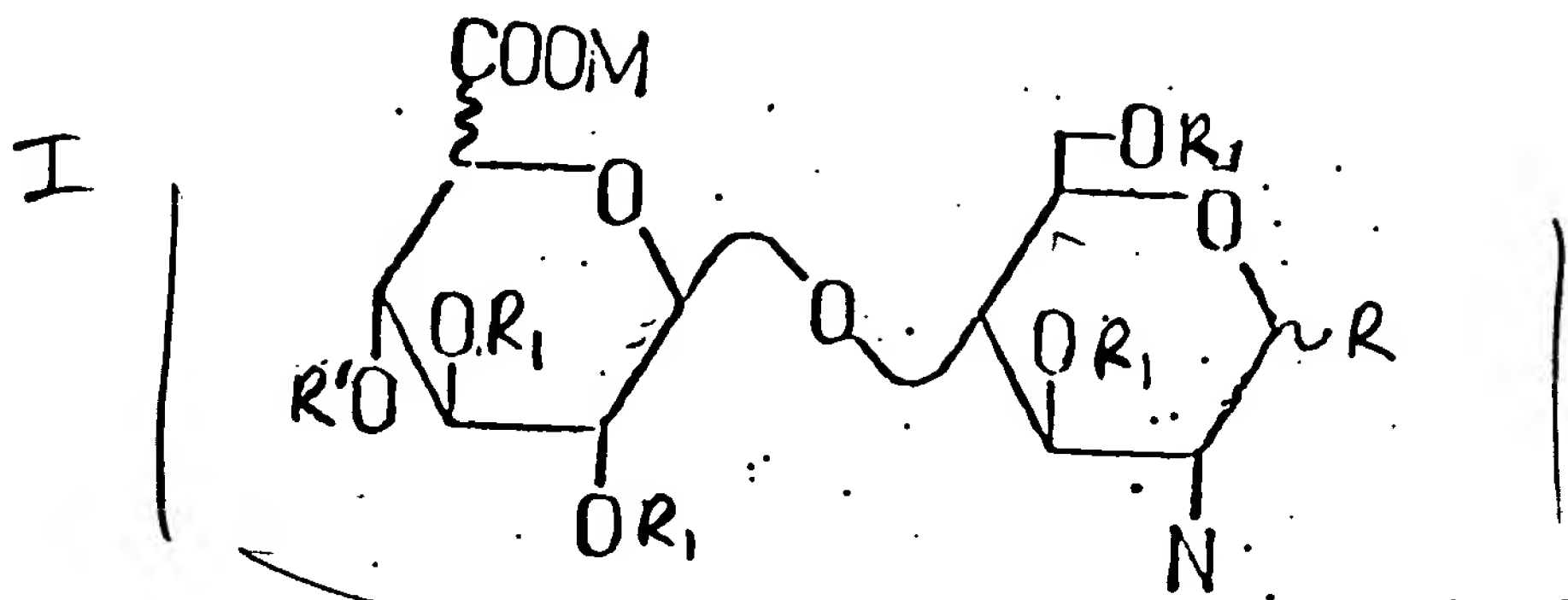
~~19~~ <sup>14</sup> 182. The process of claim ~~148~~ wherein the reactive group is O-lower imidoyl and the condensation reaction is carried out in the presence of a catalyst at a temperature below or equal to 0 degrees centigrade.

~~43~~ <sup>43</sup> 183. A process for selectively positioning sulfate groups or phosphate groups on a protected heparinic polysaccharide having from 2-12 units, which protected heparinic polysaccharide is comprised of alternating units of a first unit and a second unit wherein the first unit is selected from the group consisting of a D-glucosamine, a neutral sugar analog of D-glucosamine, and a desoxy sugar analog of D-glucosamine, and wherein the second unit is selected from the group consisting of a uronic acid, a neutral sugar analog of uronic acid, and a desoxy sugar analog of uronic

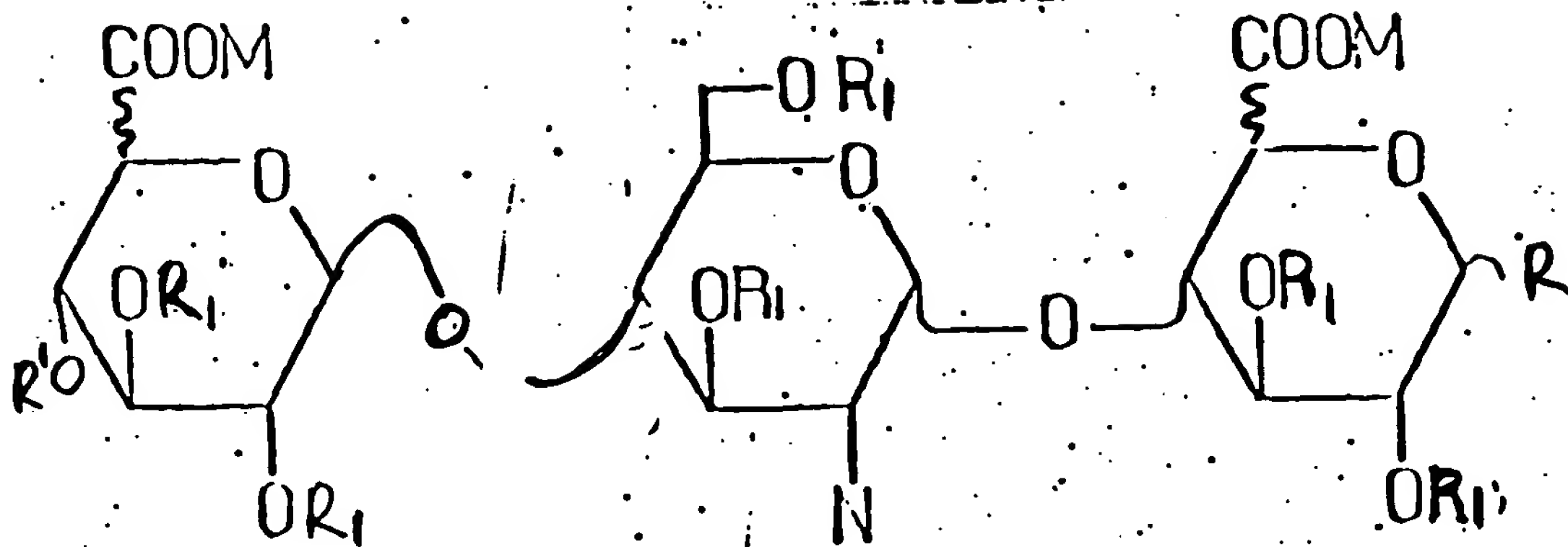
II  
acid, further wherein any uronic acid is selected from the group consisting of D-glucuronic acid and L-iduronic acid, the first and second unit being linked in the manner found in heparin and having at least on each as substituents of semi-permanent protecting groups, permanent protecting groups, other protecting groups which form an ester at the carboxyl groups of the uronic acid units, and nitrogen containing groups at carbon 2 of the D-glucosamine units wherein the permanent protecting groups are stable and do not migrate to other carbon positions during removal of the semi-permanent protecting groups and the introduction of functional groups, which process comprises the steps of

- a) removing the semi-permanent protecting groups,
- b) introducing functional groups in place of the semi-permanent protecting groups, which functional groups are selected from the group consisting of  $-O-SO_3$  groups and  $-O-PO_3$  groups, and
- c) removing the permanent protecting groups and converting the nitrogen containing group into an amine group.

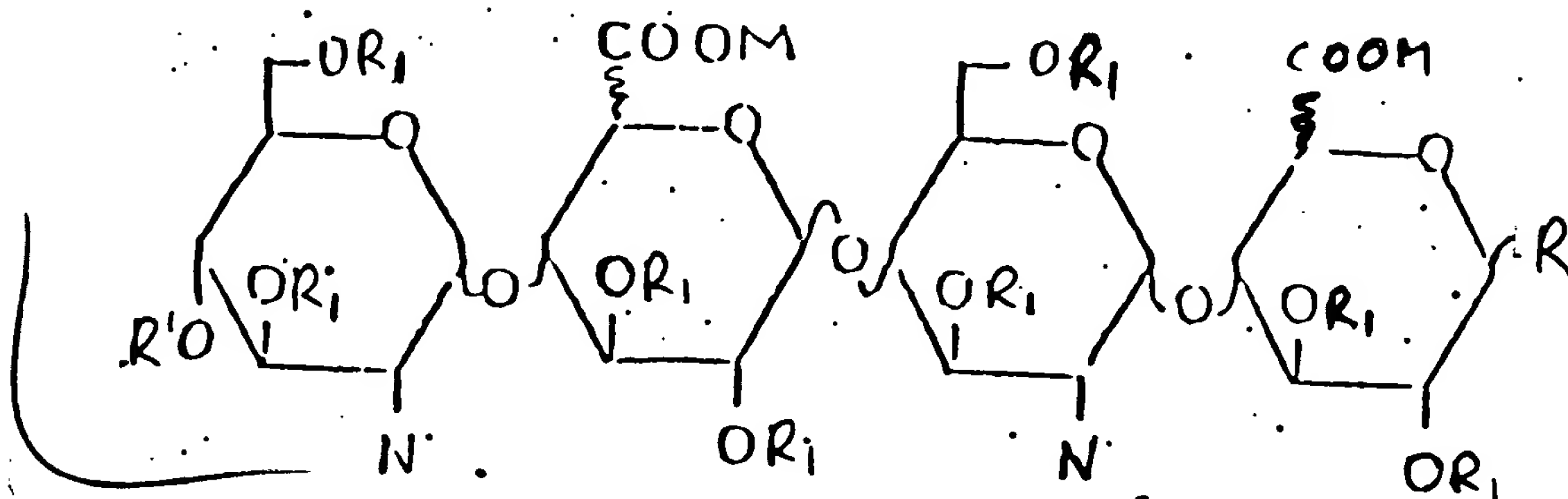
44  
~~184~~. A substantially pure compound of a single structure, which compound is selected from the group consisting of:



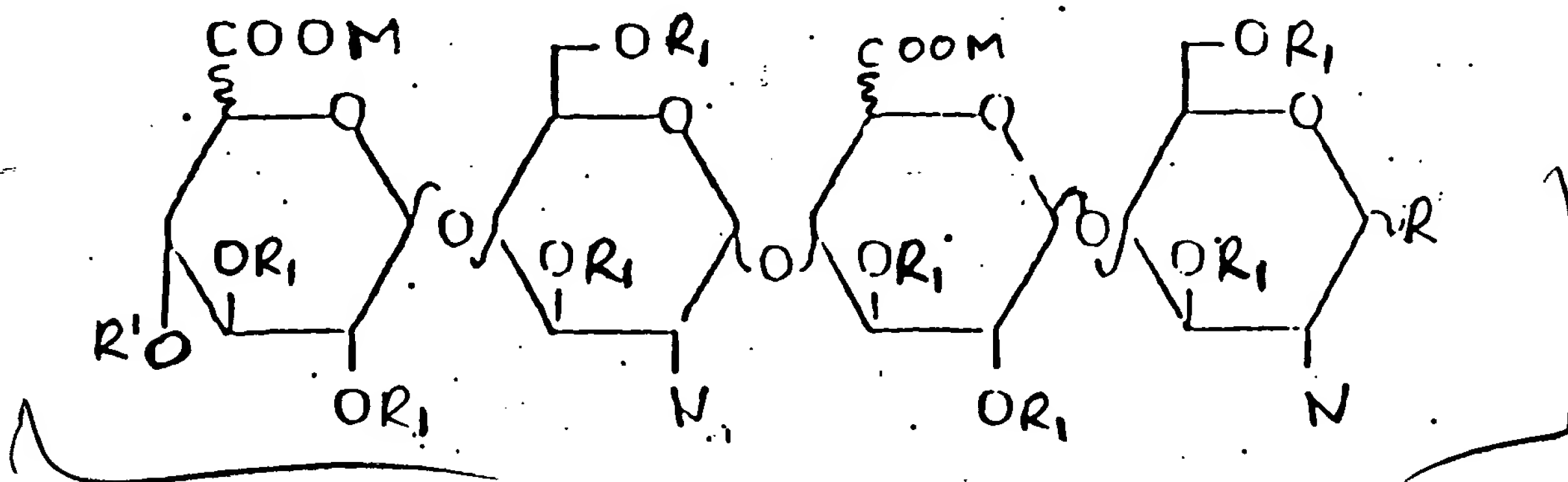
VI



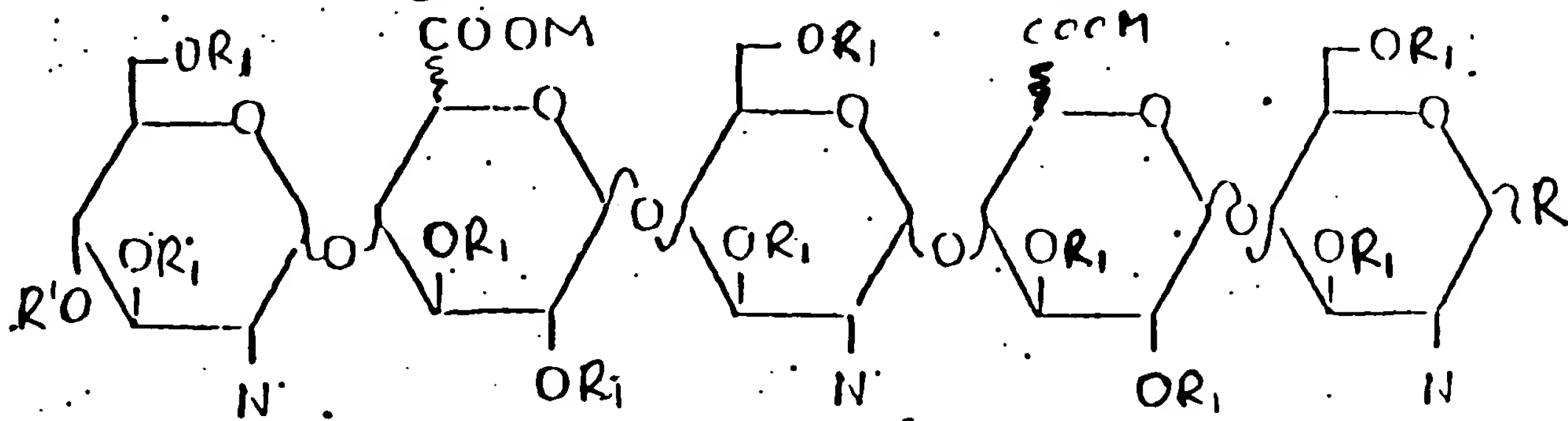
VII



VIII

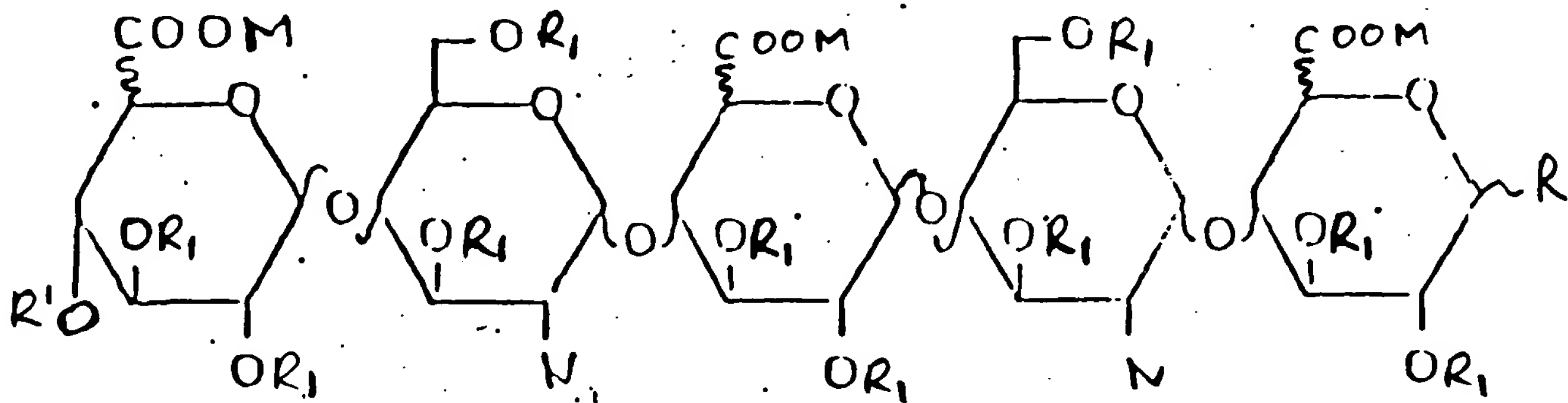


IX

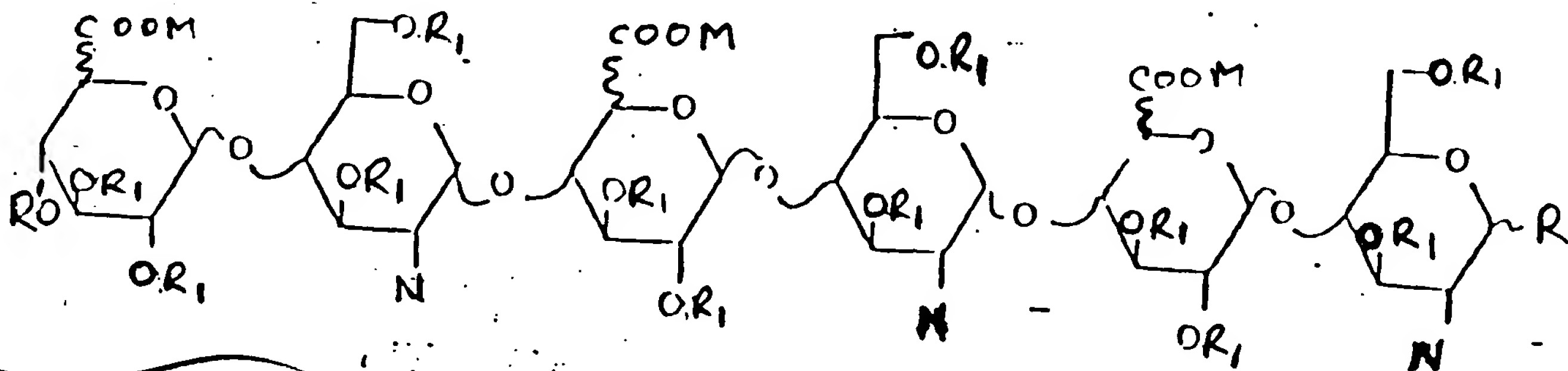


II

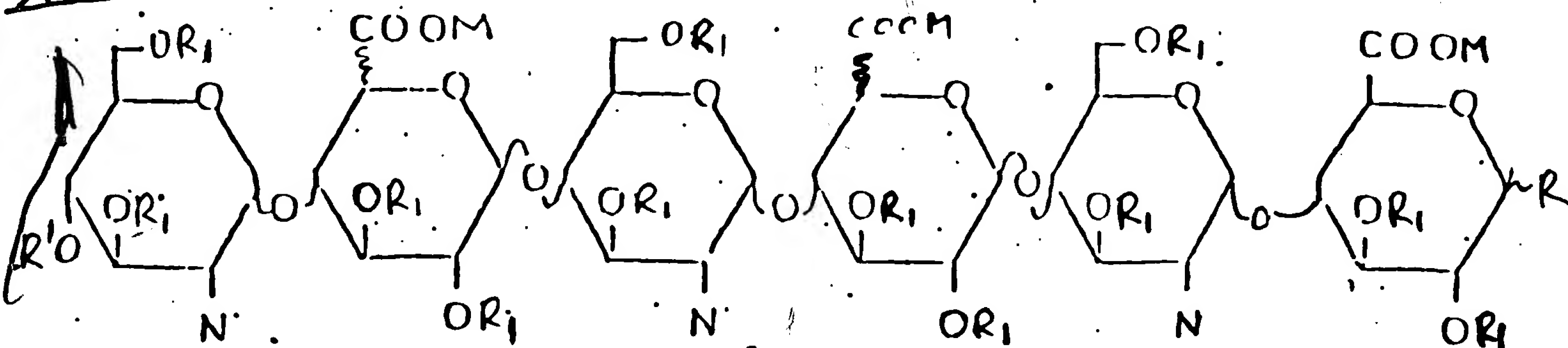
X



XI

+ 3H<sub>2</sub>O

XII



wherein

$R_1$  substituents are not the same, and are selected from the group consisting of

I

a) semi-permanent protecting groups which semi-permanent protecting groups are removable in the presence of permanent protecting groups, are stable during any condensation employed to obtain the compound and allow a stereospecific linkage during the condensation, and are stable during removal of any temporary group,

b) permanent protecting groups which permanent protecting groups are stable and do not migrate to different carbon positions during removal of the semi-permanent protecting groups and the introduction of functional groups to replace the semi-permanent protecting groups, which functional groups are selected from the group consisting of  $SO_3$  groups and  $PO_3$  groups, and which permanent protecting groups also are removable in the presence of the functional groups, are stable during the condensation, and which allow a stereospecific linkage during the condensation, and which permanent protecting groups are stable during removal of any temporary protecting group,

M is a protecting group which forms an ester at the carboxyl groups, and is stable during any condensation employed to obtain the compound,



N is a nitrogen containing group which may be treated to form an amine, and which allows a stereospecific linkage during any condensation employed to obtain the compound,

R is selected from the group consisting of:

a) a temporary protecting group which can be removed in the presence of the semi-permanent protecting groups and permanent protecting groups in order to permit elongation of the compound and which is stable during any condensation employed to obtain the compound,

b) a permanent protecting group,

c) a reactive group which can be employed in order to perform a condensation to form a 1-4 linkage as found in heparin in order to elongate the compound, and which reactive group was positioned following removal of a temporary protecting group and which allows a stereospecific linkage during the condensation,

d) an inert protecting group, which is stable during removal of the temporary protecting groups, semi-permanent protecting groups and permanent protecting groups, and

R' is selected from the group consisting of

a) a temporary protecting group,

b) a permanent protecting group, and

c) an OH group.

45 185. The substantially pure compound of claim 184 <sup>43</sup>  
wherein the compound can be elongated and R is selected from the  
group consisting of a temporary protecting group and a reactive  
group.

46 186. The substantially pure compound of claim 184 <sup>43</sup>  
wherein the compound can be elongated and R' is selected from the  
group consisting of a temporary protecting group and OH.

II 50 187. A substantially pure compound of a single structure,  
which compound is selected from the group consisting of:

Compounds I, III, V, VI, VII, VIII, IX, X, XI and XII wherein

R<sub>1</sub> substituents are not the same, and are selected from  
the group consisting of

- a) OH groups, and
- b) permanent protecting groups, which permanent  
protecting groups are stable and do not migrate to  
different carbon positions during removal of the semi-  
permanent protecting groups and the introduction of  
functional groups to replace the semi-permanent  
protecting groups, which functional groups are selected  
from the group consisting of SO<sub>3</sub> groups and PO<sub>3</sub> groups,  
which permanent protecting groups also are removable in  
the presence of the functional groups, are stable during  
the condensation, and which allow a stereospecific  
linkage during any condensation employed to obtain the

compound, and which permanent protecting groups are stable during removal of any temporary protecting group,

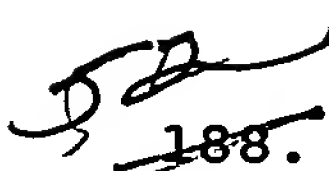
M is a protecting group which forms an ester at the carboxyl groups, and is stable during any condensation employed to obtain the compound,

N is a nitrogen containing group which can be treated to form an amine, and which allows a stereospecific linkage during any condensation employed to obtain the compound,

R is selected from the group consisting of:

- a) a permanent protecting group,
- b) an inert protecting group which is stable during removal of the temporary protecting groups, semi-permanent protecting groups and permanent protecting groups, and

R' is a permanent protecting group.

 188. A substantially pure compound of a single structure, which compound is selected from the group consisting of:

Compounds I, III, V, VI, VII, VIII, IX, X, XI and XII wherein

R<sub>1</sub> substituents are not the same, and are selected from the group consisting of

- a) functional groups which are selected from the group consisting of SO<sub>3</sub> groups and PO<sub>3</sub> groups,
- b) permanent protecting groups, which permanent protecting groups are stable and do not migrate to

different carbon positions during removal of the semi-permanent protecting groups and the introduction of the functional groups to replace semi-permanent protecting groups, which permanent protecting groups also are removable in the presence of the functional groups, are stable during the condensation, and which allow a stereospecific linkage during any condensation employed to obtain the compound, and which permanent protecting groups are stable during removal of any temporary protecting group,

*I*  
M is a protecting group which forms an ester at the carboxyl groups, and is stable during any condensation employed to obtain the compound,

N is a nitrogen containing group which can be treated to form an amine, and which allows a stereospecific linkage during any condensation employed to obtain the compound,

R is selected from the group consisting of:

- a) a permanent protecting group,
- b) an inert protecting group which is stable during removal of the temporary protecting groups, semi-permanent protecting groups and permanent protecting groups, and

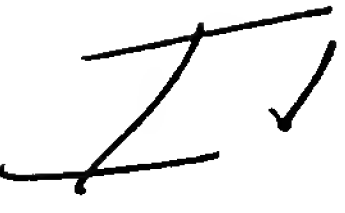
R' is a permanent protecting group.

54 189. A substantially pure compound of a single structure, which compound is selected from the group consisting of:

Compounds I, III, V, VI, VII, VIII, IX, X, XI and XII wherein

$R_1$  substituents are not the same, and are selected from the group consisting of

- a) functional groups which are selected from the group consisting of  $SO_3$  groups and  $PO_3$  groups, and
- b) OH groups,

 M is a protecting group which forms an ester at the carboxyl groups, and is stable during any condensation employed to obtain the compound,

N is the same or different and is selected from the group consisting of

- a) an amine,
- b) NH acetyl, and
- c) NH  $SO_3$

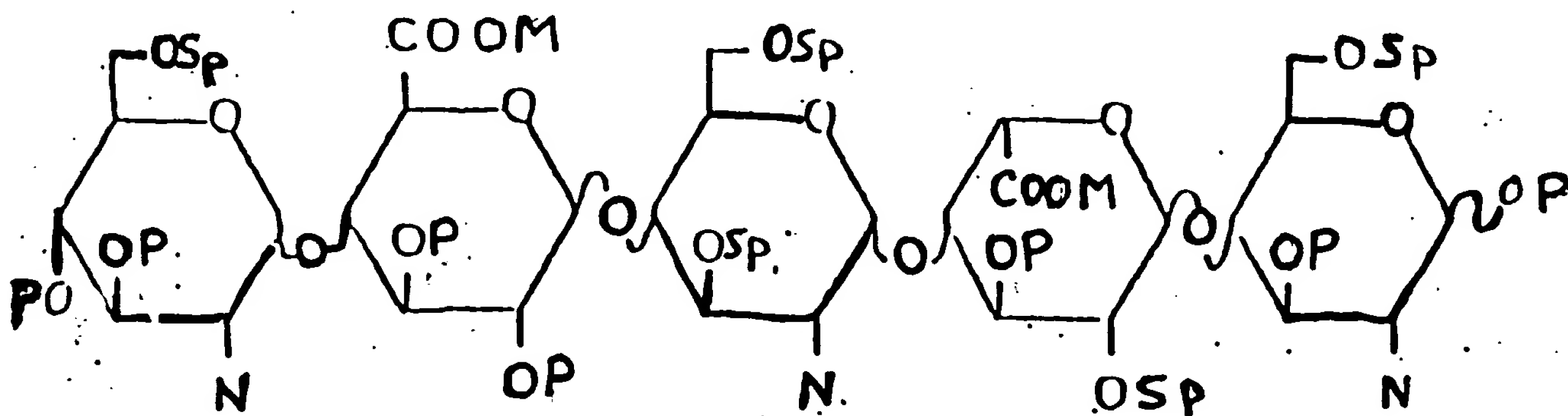
R is selected from the group consisting of:

- a) An OH group,
- b) an inert protecting group which is stable during removal of the temporary protecting groups, semi-permanent protecting groups and permanent protecting groups, and

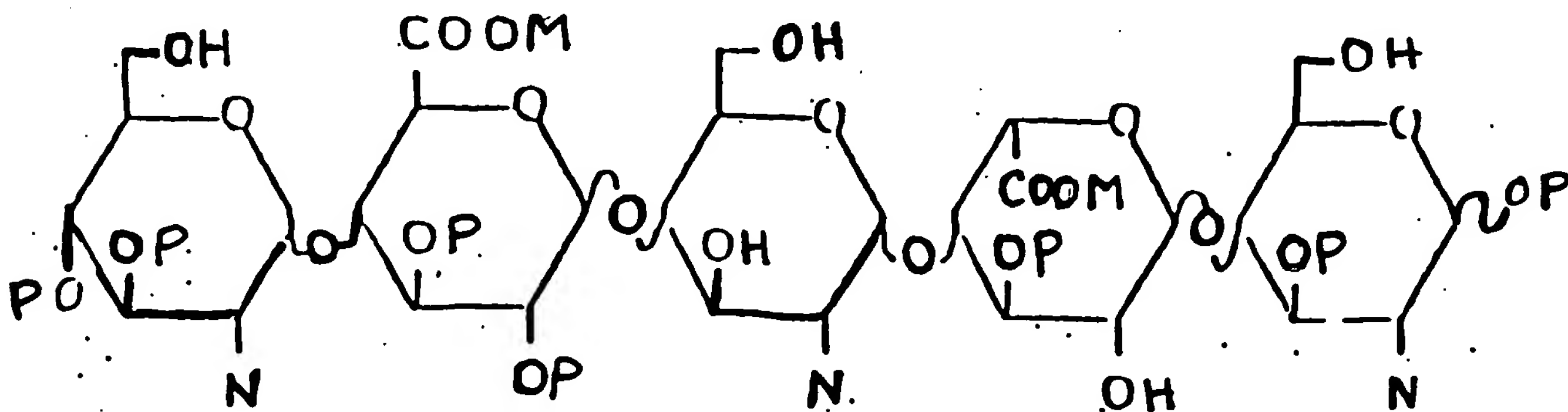
$R'$  is OH.

~~56~~ 190. The substantially pure compound of claim ~~189~~ <sup>54</sup> wherein N is selected from the group consisting of NH acetyl and NH SO<sub>3</sub> and wherein M is removed and the compound forms an anion.

~~47~~ 191. The substantially pure compound IX of claim ~~184~~ <sup>46</sup> wherein the R<sub>1</sub> substituents are selected from the group consisting of semi-permanent protecting groups and permanent protecting groups, wherein R is a permanent protecting group, wherein R' is a permanent protecting group, and wherein the semi-permanent protecting groups are sp groups and wherein the permanent protecting groups are p groups, which compound has the formula

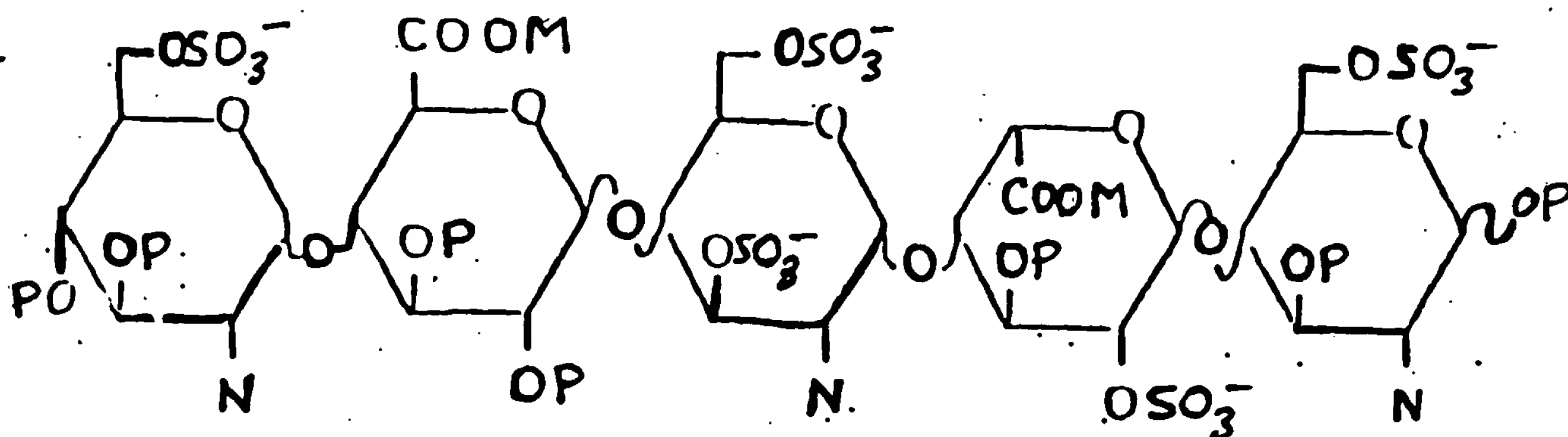


~~51~~ 192. The substantially pure compound IX of claim ~~187~~ <sup>50</sup> wherein R<sub>1</sub> substituents are selected from the group consisting of OH groups and permanent protecting groups, wherein R is a permanent protecting group, wherein R' is a permanent protecting group, and wherein the permanent protecting groups are p groups, which compound has the formula

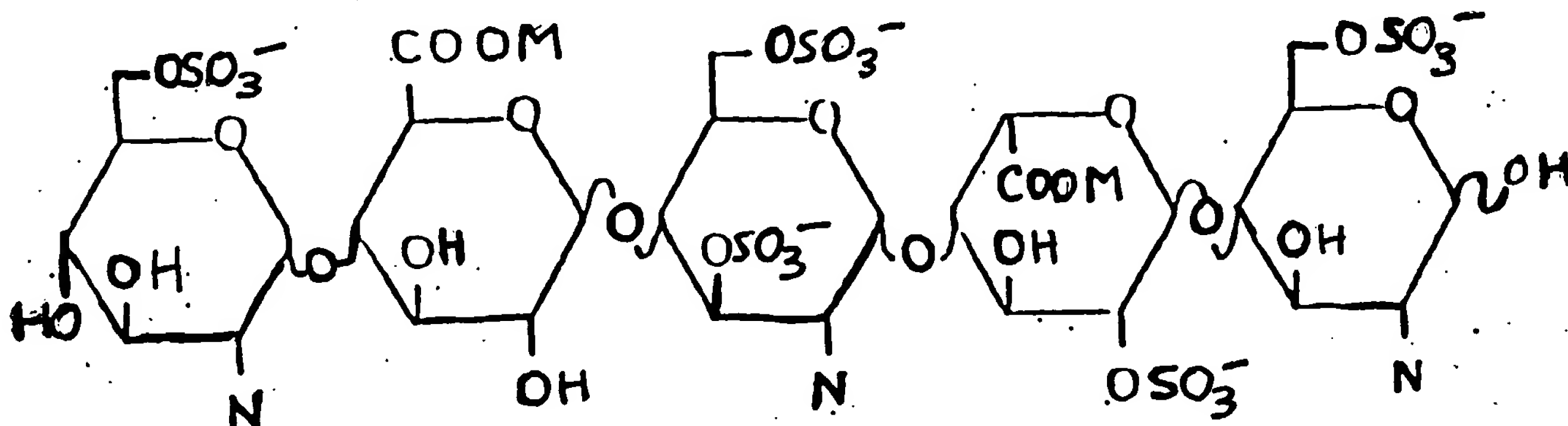


52

~~53~~ 193. The substantially pure compound IX of claim ~~188~~ wherein  $R_1$  substituents are selected from group consisting of  $SO_3$  groups and permanent protecting groups, wherein R is a permanent protecting group, and wherein  $R'$  is a permanent protecting group, and wherein the permanent protecting groups are p groups, which compound has the formula

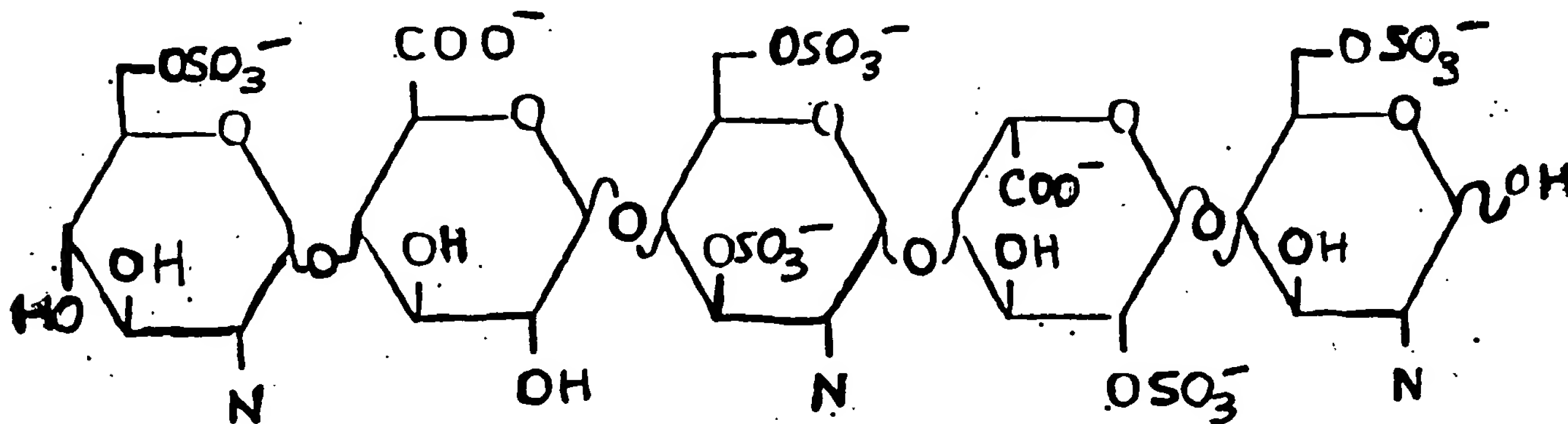


~~55~~ 194. The substantially pure compound IX of claim ~~189~~ wherein  $R_1$  substituents are selected from the group consisting of  $SO_3$  groups and OH groups, wherein R is an OH group,  $R'$  is an OH group, and N is selected from the group consisting of an amine, NH acetyl, and NH  $SO_3$  which compound has the formula





57 ~~195~~. The substantially pure compound IX of claim ~~190~~ <sup>56</sup> wherein sp is SO<sub>3</sub> and p is OH, and N selected from the group consisting of NH acetyl and NH SO<sub>3</sub> and M is removed to form an anion of the compound, which compound has the formula



48 ~~196~~. The substantially pure compound of any of claims ~~184~~ <sup>44</sup>,  
~~45~~ <sup>46</sup> ~~185~~ or ~~186~~  
 wherein

- a) any nitrogen containing group is selected from the group consisting of
  1. N<sub>3</sub>,
  2. NH - lower acyl, and
  3. (NHCO - lower arylalkyl;)
- b) any protecting group at the carboxyl is selected from the group consisting of
  1. lower alkyl, and
  2. aryl;
- c) any semi-permanent protecting group is lower acyl;
- d) any temporary protecting group is selected from the group consisting of

1. -O-lower acyl,
2. -O-allyl,
3. -O-propenyl,
4. halogenated -O-lower acyl, and
5. -O-p-methoxybenzoyl;

e) any permanent protecting group is benzyl,  
f) any reactive group is selected from the group consisting of

1. halogen,
2. lower imidoyl, and
3. an orthoester formed between the carbon 1 and

carbon 2 positions where the reactive group occupies a position at carbon 1 of a uronic acid unit,

g) any inert protecting group is -O-lower alkyl, and  
h) any functional group is  $\text{SO}_3$ .

49

~~197.~~ The substantially pure compound of claim ~~186~~ wherein

48

a) any nitrogen containing group is selected from the group consisting of

1.  $\text{N}_3$ ,
2.  $\text{NH}$  - acetyl, and
3.  $\text{NHCO}$  - benzyl;

b) any protecting group which forms an ester at the carboxyl is methyl;

c) any semi-permanent group is acetyl;

d) any temporary group is selected from the group consisting of

1. -O-acetyl,
2. -O-benzyl,
3. -O-allyl,
4. -O-propenyl,
5. monochloro-O-acetyl,
6. trichloro-O-acetyl, and
7. -O-p-methoxybenzoyl;

e) any permanent group is benzyl;

f) any reactive group is selected from the group consisting of

1. Br,
2. Cl,
3. (an orthoester having between 3 and 6 carbons, and
4. C(NH)CCl<sub>3</sub>;

g) any inert blocking group is an -O-lower alkyl group having between 1 and 4 carbons, and

h) any functional group is SO<sub>3</sub>.

58  
~~198.~~ A substantially pure heparin chain of a single structure comprised of 2 to 12 saccharide units.

59  
~~199.~~ A substantially pure oligosaccharide of a single structure comprised of 2 to 12 alternating D-glucosamine and